Botulinum Toxin Type A

Subjects: Cell Biology

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Botulinum neurotoxin A (BoNT-A) which is generally known as anti-contraction of muscles has been reported as a successful treatment in various types of chronic ulcers.

BoNT-A ischemia neuromodulators

1. Introduction

Normal physiologic wound healing happens in three highly integrated and overlapping phases: inflammation, proliferation, and remodeling [1][2][3]. Good blood circulation, proper immune function, and adequate nutrition are required for optimum healing [1][4]. When any phase is disrupted, healing might be impeded and turned into chronic ulcers which are generally known as loss of normal skin integrity for more than 6 weeks [5][6][7]. Many factors attribute to retard wound healing. For instance, vascular insufficiency, neurologic abnormalities, nutritional deficiencies, advanced age, chronic diseases, and local wound infection can all disrupt the healing process [1][8][9][10]. Not only removing primary underlying causes but also following principles of wound care such as appropriate tissue debridement and optimal moist environment for normalization of the wound healing process is essential [1][11][12]. However, unsatisfied outcomes still exist [6][13][14].

Botulinum toxin is a neurotoxin produced by *Clostridium botulinum* [15]. It has long been known for its action in preventing the release of the neurotransmitter acetylcholine from axons at the neuromuscular junction and temporally inhibiting muscle contraction. So far, there are seven serotypes (A, B, C1, D, E, F, and G) [16]. Serotypes A and B are currently in clinical usage, but botulinum neurotoxin A (BoNT-A) is the most commonly used [15][16]. Concerning temporary muscle paralysis capability, wide clinical treatment has been adopted [16][17][18]. Apart from inhibiting acetylcholine release from a presynaptic neuromuscular junction, studies found that BoNT-A can reduce skin inflammation by inhibiting mast cell degranulation and blocking cholinergic stimuli to apocrine and eccrine glands [19].

2. Mechanism of BoNT-A on Wound Healing

Normal physiologic wound healing is a dynamic process consisting of different continuous, overlapping, and precisely programmed phases [1][3][11]. Any disruption in the process leads to abnormal wound healing or chronic unhealed ulcers [12]. The literature review found BoNT-A can enhance wound healing in various types of ulcers. Several studies that investigated mechanisms of BoNT-A on wound healing found that BoNT-A decreased inflammatory cell infiltration during the inflammatory phase [20][21][22]. Inhibition of mast cell degranulation and

reduction in number were reported [19][23]. Reduction in vascular permeability and exudation of neutrophils and macrophages were also observed. Consequently, pus deposition on ulcers was reduced [24]. Furthermore, during the proliferative phase, it could enhance blood flow and promote vascular sprouting by increasing expression in CD31+, ∝SAM (+) pericytes, as well as fibroblasts [25][26][27][28]. It could be due to a reduction of reactive oxygen species (ROS) release and endothelial nitric oxide synthase (eNOS) in the hypoxic area [25][29]. Altogether, granulation tissue was created and filled the wound. It also can inhibit releasing norepinephrine resulting in vasodilatation and increasing oxygenation to the wound [30]. In the period of the remodeling phase, lower expression of TGF-β1 by BoNT-A was found which reduces the risk of fibrosis and scar formation [24]. **Figure 1** shows a mechanism of BoNT-A in wound healing for comprehensive understanding.

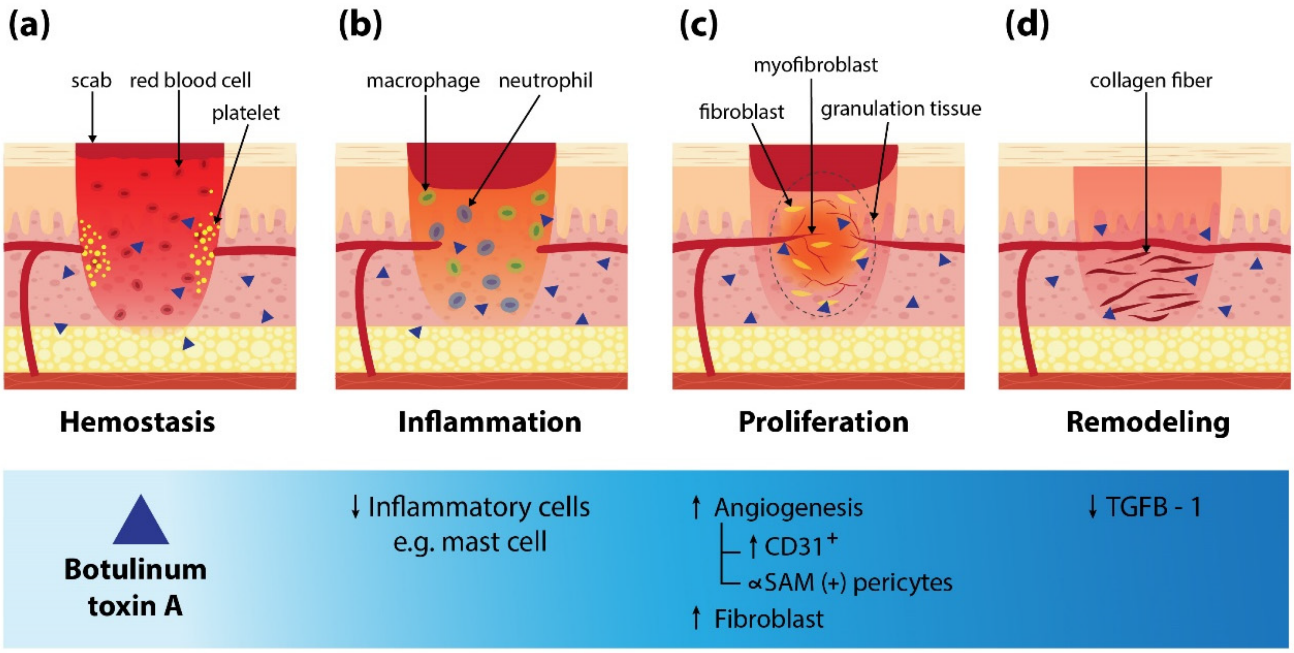

Figure 1. The proposed mechanisms of botulinum neurotoxin A in the wound healing process. TGFβ-1: Transforming Growth Factor β-1.

For miscellaneous types of chronic ulcers, BoNT-A has been proposed to hasten wound healing by inhibiting sweat-induced maceration of the fragile epidermis to optimize the wound environment [31].

3. BoNT-A for Various Types of Skin Ulcers

Ischemic Ulcers Secondary to Raynaud's Phenomenon (RP)

Although numerous publications demonstrated a positive effect of BoNT-A on RP [32][33][34][35][36], this entry will mainly focus on patients who had RP-associated ulcers. Based on the literature search, 12 articles (case reports, retrospective case series, and prospective case series) with a total of 104 patients who had RP-associated ulcers were identified (**Table 1**) [37][38][39][40][41][42][43][44][45][46][47][48]. Patients have been suffering from RP symptoms (pain,

loss of function, disfigurement, and so forth) and chronic ischemic nonhealing ulcers. Moreover, some underwent sympathectomy but the clinical of ulcers did not improve [37].

Table 1. A summary of articles on the treatment outcome of chronic ischemic ulcers secondary to Raynaud's phenomenon.

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% (NSS)	BoNT-A Dose/Location	Follow-Up Period	Results	Reinjection (Interval)	Comments
Quinatana Castanedo et al., 2020 [40]	Case report	1 (female)	15	NR	NR	32 units/Foot	4 weeks	- Complete resolution - Complete epithelization	Yes (every 12 months)	
Habib et al., 2020 [47]	Case series	3 (female)	23–50	NR	NR	32 units/Hand	1 week	- 75% (2/3) completely free of symptoms - No effect (1 case)	No	
Min et al., 2020 [44]	Case report	1 (male)	48	Medytoxin® (Medytox, Seoul, Korea)	10 units/0.1 mL	10 units/Hand	12 weeks	- Healed	Yes (weekly for 3 weeks)	
Souk and Kim, 2019 [48]	Case report	2 (female)	50 and 62	Medytoxin® (Medytox, Seoul, Korea)	10 units/0.1 mL	10 units/Hand	8 weeks	- Healed and almost healed	Yes 2/2 (4 and 5 weeks, 7 and 8 weeks)	
Garrido-Rios et al., 2018 [41]	Case report	1 (female)	30	NR	8–10 units/0.4 mL	80–100 units/Hand	2 months	- Reduction in necrotic area	No	
Medina et al., 2018 [45]	Retrospective case series	15 (female 14/male 1)	35–71	Botox® (Allergan Pharmaceuticals	100 units/5 mL	Average 45 units/Hand	3 years	- Significantly decreased in 1 month	Yes 6/15 (annually)	4/15 temporary decrease intrinsic

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% (NSS)	BoNT-A Dose/Location	Follow-Up Period	Results	Reinjection (Interval)	Comments
				Ltd., Westport, Ireland)				- Significantly decreased in 1 month - 71% (5/7) patients healed at 3 months		muscle strength
Blaise et al., 2017 [43]	Case report	1 (female)	55	NR	NR	100 units/Hand	4 months	- Completely healed - Increased skin blood flow	No	
Motegi et al., 2016 [42]	Prospective, case series	10 (NR)	62.5 (±3.5)	Botox® (Allergan Pharmaceuticals Ltd., Westport, Ireland)	20 units/0.1 mL	10 units/Hand	16 weeks	- Significant reduction at 2 weeks and throughout the study - Significant reduction at 2 weeks and throughout the study - Significantly enhanced at 4 weeks - 100% (5/5) healed within	No	

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% (NSS)	BoNT-A Dose/Location	Follow-Up Period	Results	Reinjection (Interval)	Comments
								12 weeks		
Zhang et al., 2015 [38]	Retrospective case series	10 (female 5/male 5)	48–91	Botox® (Allergan Pharmaceuticals Ltd., Westport, Ireland)	100 units/5 mL	60 units/Hand	6 months (average)	- 100% Improvement, significant improvement of the PSV - Significantly increased on palms and fingers - Significant decrease in pain, numbness, stiffness, swelling - 50% (1/2) healed at 3.5 weeks	No	
Smith et al., 2012 [37]	Case report	1 (female)	52	NR	5 units/0.1 mL	100 units/Hand	3 months	- Improvement blood flow - Decrease - 67% (6/9) healed - 22% (2/9) partially healed	No	Mild, nonlimiting thenar muscle weakness

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adopted was toxin 20 units to 0.9% NSS 1 mL [41][42][45][49]. Two reports from Korea used BoNT-A 100 units to 0.9% NSS 1 mL [44][48]. The toxin concentration of other studies was BoNT-A 50 units to 0.9% NSS 1 mL [37][39] and BoNT-A 5 units to 0.9% NSS 1 mL [46], respectively.

There was no standard guideline regarding the site of injection. Nevertheless, three areas of injection were proposed to target neurovascular bundles on palms: (1) Base of digits at web spaces (i.e., bifurcation of the superficial digital arteries) [37][38][39][45][47]; (2) Palmar aspect of the hand, just proximal to the A1 pulley, targeting the neurovascular bundles [37][42][46]; and (3) Both sides of proximal hand (i.e., radial and ulnar arteries) [38][39]. Most studies adopted either option 1 or 2 or a combination [37][42][45][46][47]. Two retrospective studies injected all three areas [38][39]. Injection patterns are shown in **Figure 2**. There were two reports with foot ulcers injected at interdigital web space oriented toward the neurovascular bundle [40][41].

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% (NSS)	BoNT-A Dose/Location	Follow-Up Period	Results	Reinjection (Interval)	Comments
Neumeister. 2010 [46]	Retrospective case series	33 (female 19/male 14)	18–72	Botox® (Allergan Pharmaceuticals Ltd., Westport, Ireland)	100 units/20 mL	50 units/Hand	6 years	- 85% (28/33) relieved - Improvement in perfusion - 100% healed within 2 months	Yes 7/33 (not reported)	- 3 patients had temporary intrinsic muscle weakness that lasted 2 months
Fregene et al., 2009 [39]	Retrospective case series	26 (female 14/male 12)	60.7 (±1.9)	Botox® (Allergan Pharmaceuticals Ltd., Westport, Ireland)	100 units/2 mL	Average 77 units/Hand	18 months (average)	- Significant mean 35% reduction - Significant color improvement in the female and smoker's subgroup - Significant increasing - 48% (11/23) healed (average healing time 9.5 weeks)	No	- Some reported intrinsic muscle weakness and 1 dysesthesia digit which resolved completely by 5 months

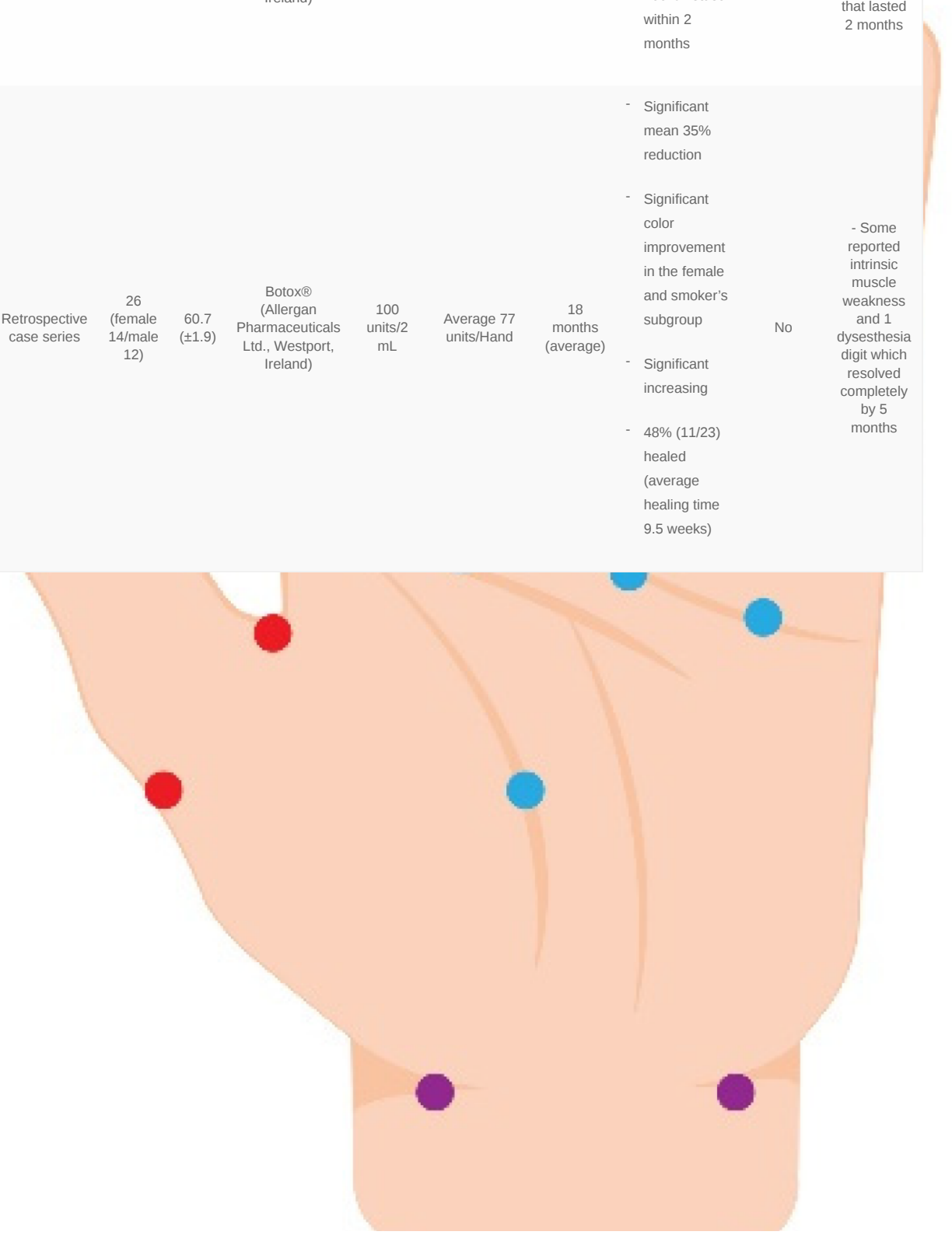

Figure 2. The BoNT-A injection patterns for Raynaud's phenomenon-associated ulcer. Red dots represent the base of the digit injection pattern. Blue dots identify the palmar injection pattern. Purple dots identify the proximal hand injection pattern.

Parameters tracked outcomes consisted of objective and subjective measurements. Among objective measurements, arterial blood flow was evaluated by using ultrasonography or doppler perfusion imaging, while skin surface temperature was assessed by a thermometer or temperature recovery after ice-bath immersion [42]. In terms of subjective assessment, a visual analog scale (VAS) for pain, general RP symptoms using Raynaud's score [50], digital color changes, and patient global assessment were used. However, for healing ulcers, no wound assessment scale was used. Investigators merely monitored ulcers as complete, partial healing, and no response.

Of a total of 104 cases with RP-associated ulcers, 81% (84 of104 cases) had healed completely. Immediate improvement of blood flow, pain, temperature, and color after injection was noted [37][41]. Raynaud's score and VAS for pain decreased at 2 weeks and persisted until 16 weeks after injection [42].

One case report presented a 55-year-old woman who was diagnosed with limited cutaneous systemic sclerosis with refractory multiple digital ulcers. She failed many medical treatment regimens and underwent amputation once. During the period of critical ischemic digits which further amputation was nearly executed, BoNT-A was challenged, and digits were rescued with complete wound healing eventually [43]. Another case report showed a 48-year-old male who was diagnosed with anti-MDA5-Ab-positive dermatomyositis with refractory digital ulcers had an improvement in ulcers after BoNT-A injection [44].

According to a 3-year follow-up study by Medina et al., 8 of 14 patients (57.1%) demonstrated a very good response at 1 month after treatment. A mild to moderate response was observed in three patients (21.4%). Of the seven patients with basal ulcers, five were completely healed at 3 months after treatment. At the end of treatment, 64.3% of patients showed an overall satisfaction level of >8 [45].

However, some patients with RP showed no response to BoNT-A injection which resulted in amputation. Therefore, the discussion with patients before employing this technique is mandatory [39][45][46].

BoNT-A for Pressure Ulcers

Administration of BoNT-A on pressure ulcers that were associated with muscle spasticity has been reported [51][52][53][54][55]. The rationale for the use of BoNT-A on pressure ulcers is to relieve muscle spasticity [56][57]. As a result, pressure ulcers are adequately accessed and omitted from repetitive trauma.

Regarding the point of injection, BoNT-A can be injected directly into abnormally contracted muscle or under electromyographic guidance [52][53][54]. The number of injection points was considered based on the size of muscles. According to a report by Insito et al., abobotulinum toxin with doses of 200 and 120 speywood unit (SU) was injected into orbicularis oris and masseter in a vegetative state patient with oromandibular dyskinesia [54]. Regarding the larger size of muscles such as Gluteal muscle, a high dosage of 660 SU was used [53]. Gupta and

Wilson reported a dosage of onabotulinum toxin ranging from 100 to 150 units per muscle [52]. Abnormal contraction or spasticity were improved as early as 1 week after treatment [5]. All ulcers were reported as complete healing with the most delayed time period of 6-month follow-up [53]. The number of treatment sessions varied from one to two sessions. A repeated treatment session might be considered in patients with partially healed ulcers to maintain the weakness of muscles. Data regarding the use of BoNT-A in pressure ulcers is summarized in **Table 2**.

Table 2. A summary of articles on the treatment outcome of other types of chronic ulcer.

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% NSS	BoNT-A Dose/Location	Follow-up Period	Results	Reinjection (Interval)	Comments
Gupta and Wilson, 2020 [52]	Case report	1 (female)	59	NR	NR	150 units for pectoralis major, 150 for elbow flexors, 100 for flexor digitorum superficialis	5 months	Completely healed ulcer	Yes (5 months)	Pressure ulcer
Insito and Basciani, 2009 [53]	Case report	1 (male)	27	Dysport®, Ipsen Limited, Slough, UK	NR	660 Speywood units (left Gluteus maximus)	6 months	Weaken muscle contraction Healed ulcer	Yes (3 months)	Pressure ulcer
Insito et al., 2008 [54]	Case report	1 (male)	73	Dysport®, Ipsen Limited, Slough, UK	NR	200 Speywood units for Orbicularis oris, 120 for Masseter	3 months	Improved dyskinetic disorder Completely healed ulcer	Yes (2 months)	Pressure ulcer

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% NSS	BoNT-A Dose/Location	Follow-up Period	Results	Reinjection (Interval)	Comments
Sillitoe et al., 2007 [55]	Letter to editors	1 (male)	58	NR	NR	NR (adductor muscle bellies lower limbs) [58]	16 weeks	Marked reduction in spasticity [58][59] Ulcers showed signs of healing Ulcers show significant improvement Ulcers fully healed	No	Pressure ulcer
Laarakker and Borah, 2020 [58]	Retrospective cohort, case series	5 (NR)	31-71	NR	NR	80–100 units (palm and wrist)	NR	All Digits were preserved	No	Traumatic ulcer
Upton et al., 2009 [59]	Letter to editors	1 (NR)	4	NR	NR	10 units (palm)	NR	The digits were rescued	No	Traumatic ulcer
Zhong et al., 2019 [60]	Case series [60]	4 (female 1/male 3)	16-78	NR	NR	32–48 units (face, leg, foot)	50 days	Ulcers healed	No	Chronic skin ulcer

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4. Practical Guidelines for Treatment

To date, a standard guideline for BoNT-A injection for chronic ulcers has not been established yet due to a lack of strong evidence that supports the efficacy of BoNT-A for skin ulcers. Based on the available data, BoNT-A might be offered to patients with chronic skin ulcers due to vascular compromised (i.e., RP-associated ulcer, pressure ulcers with vascular compromised), traumatic ulcers, etc. (**Figure 3**). BoNT-A for RP-associated ulcers seems to be the most promising efficacy and established treatment method. Nevertheless, its harmlessness and ubiquity make it worth trying for those chronic ulcers that failed standard therapy. Adverse effects were mild and temporally, an intrinsic hand muscle weakness has been reported which resolved completely within 5 months [41][43][49][50]. In terms of point of injection, the recommendation is to consider the type of ulcer including 1) ischemic ulcers: inject toward neurovascular bundles for vasodilation [41][42][43][46][49][50][51]; 2) pressure ulcers: inject into contracted and

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muscle.

Authors, Year	Study Type	N (Gender)	Age, Years (Mean or Range)	Type of BoNT-A	BoNT-A Dilution with 0.9% NSS	BoNT-A Dose/Location	Follow-up Period	Results	Reinjection (Interval)	Comments
Alsharqi et al., 2011 [61]	Correspondence	1 (male)	51	Botox® (Allergan Pharmaceuticals Ltd., Westport, Ireland)	NR	70 units (right foot)	3 months	Completely healed ulcer	Yes (3 months)	Neuropathic ulcer

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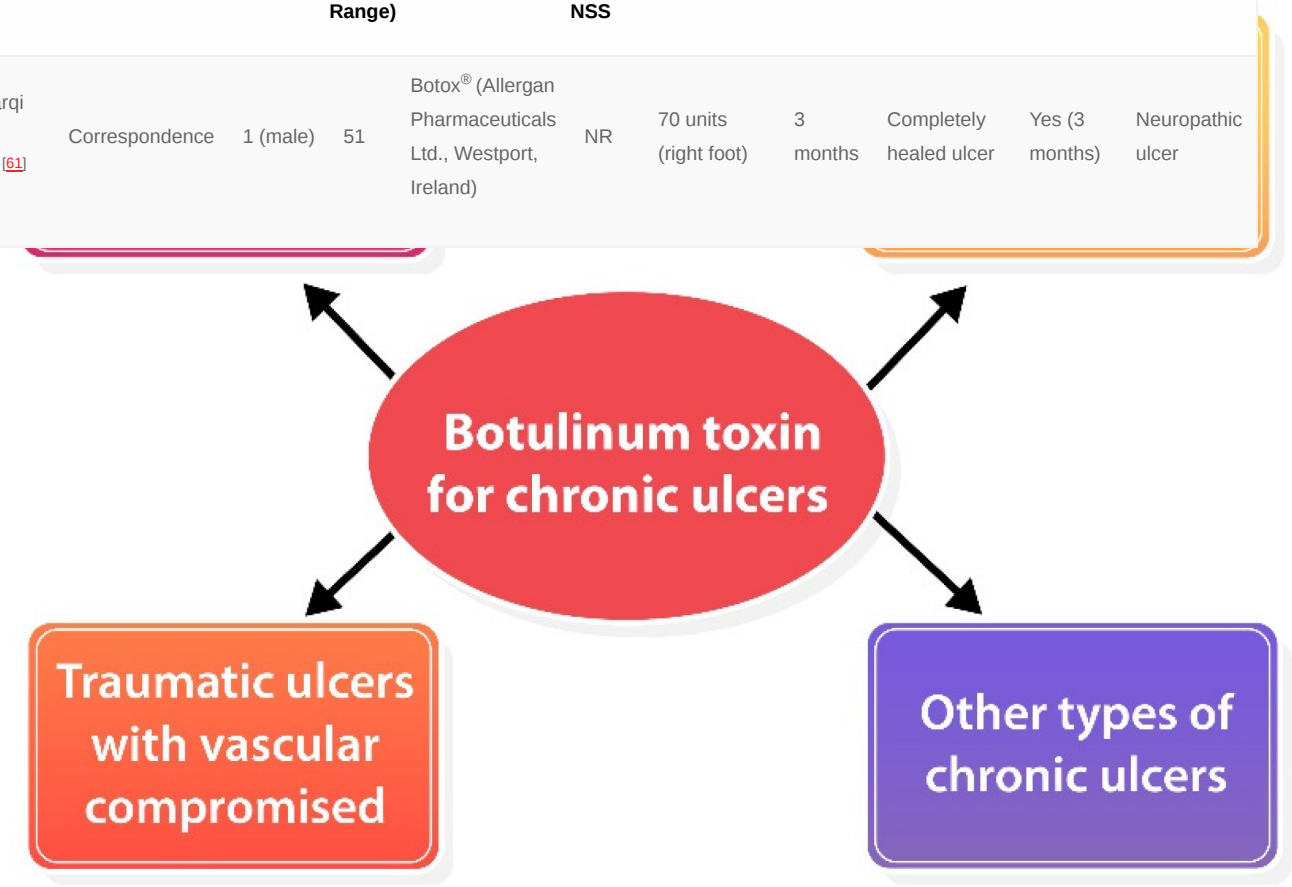

Figure 3. Potential role of BoNT-A for various types of chronic ulcers.

5. Conclusions

In summary, BoNT-A injection, a minimally invasive procedure that has a low rate of side effects can be adjunctive therapy for enhancing wound healing in various types of chronic ulcers that have been treated for underlying causes and had wound care properly as well as in ischemic ulcers associated RP in which failed conventional therapy. However, there is no randomized controlled trial study (RCT) with a large number of patients to affirm those efficacies. The amount of BoNT-A injection and the exact point of injection is still uncertain. Future randomized controlled studies should be conducted to evaluate the efficacy and safety of BoNT-A for various types of ulcers with different anatomical regions.

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